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(57) Abstract

Uridine 5'-triphosphate, or a pharmaceutically acceptable salt thereof, is useful in the symptomatic treatment of cystic fibrosis when inhaled into the lungs. Suitable pharmaceutical compositions for use in such treatment include solutions for nebulization, non-pressurized powders and pressurized aerosols.

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PHARMACEUTICAL COMPOSITION CONTAINING URIDINE 5'-TRIPHOSPHATE FOR THE TREATMENT OF CYSTIC FIBROSIS

This invention relates to a new method of symptomatic treatment of cystic fibrosis using a known compound, and to pharmaceutical compositions containing that compound.

A major symptom of cystic fibrosis is the accumulation of thick mucus in the airways, particularly the lungs, which is difficult for a patient to expectorate. This thick mucus is readily colonized by bacteria, for example *Pseudomonas aeruginosa*, leading to chronic infection and scarring of the lung tissue. The resulting impairment of lung function is the usual cause of death, and the majority of patients die before reaching 20 years of age.

At present, there are no medicaments available for the treatment of cystic fibrosis.

It has recently been reported (at the 1990 Cystic Fibrosis Conference by R C Boucher et al) that *in vitro* administration of adenosine 5'-triphosphate (hereinafter referred to as ATP) to airway epithelium results in the secretion of chloride ion.

Uridine 5'-triphosphate (hereinafter referred to as UTP) has been indicated in the treatment of neuralgia and related disorders, and is present in a lyophilized powder sold under the name 'Mionevrasi Forte' in Italy. In use, the powder is dissolved and injected intramuscularly.

It has now been found that when cystic fibrosis patients inhale UTP, or a pharmaceutically acceptable salt thereof, into their lungs, a thinning of the mucus in the airways is observed, enabling better clearance of the mucus and avoidance of bacterial infections which eventually lead to death.

According to the present invention, there is provided a pharmaceutical composition adapted for inhalation to the lungs, comprising UTP, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier. The composition may be adapted for inhalation to the lungs to the exclusion of all other modes of administration.

Pharmaceutically acceptable salts of UTP include alkali and alkaline earth metal salts, for example sodium, calcium, and ammonium salts. A specific salt which may be mentioned is the trisodium salt, particularly its dihydrate.

Pharmaceutical compositions according to the invention include solutions for nebulization, non-pressurized powders and pressurized aerosols.

Preferably, solutions for nebulization are aqueous solutions, more preferably isotonic aqueous solutions. The pH of such a solution is preferably in the range 6-8, for example 7. Preferred concentrations of UTP, or a pharmaceutically acceptable salt thereof, in a solution for nebulization are in the range $5x10^{-4}$ to $5x10^{-5}$M, for example $1x10^{-4}$M.

In non-pressurized powder and pressurized aerosol compositions UTP, or a pharmaceutically acceptable salt thereof, preferably has a mass median diameter in the range 1-10μm, more preferably 2-4μm. Such fine particles are able to penetrate deeply into the lungs, allowing a lower dosage of drug to be administered for an equivalent and longer lasting effect. Particles of UTP, or a pharmaceutically acceptable salt thereof, within the above range of mass median diameters form a second aspect of the invention.

Particles according to the second aspect of the invention may be prepared by grinding or milling using conventional methods, and are preferably dried thoroughly before being incorporated into an inhalation composition.

By 'mass median diameter' is meant the diameter such that half the particulate mass is in particles of lesser diameter and half in particles of greater diameter. The mass median diameter is essentially a Stokes diameter and may be determined using a Joyce Loebl sedimentation disc centrifuge either in a two-layer or line start photometric mode (J Bagness and A Ottaway, Proc Soc Analyt Chem, Part 4, Vol 9, 1972, pages 83-86).

Non-pressurized powder compositions preferably contain a pharmaceutically acceptable carrier having a mass median diameter of up to 400μm. A preferred carrier is lactose, for example crystalline lactose. Non-pressurised powder compositions preferably contain

from 2 to 50% by weight, more preferably from 5 to 25% by weight, and particularly from 10 to 15% by weight of the active ingredient, and from 50 to 98% by weight, more especially from 75 to 95% by weight of the carrier.

Pressurized aerosol compositions will generally contain a pharmaceutically acceptable aerosol propellant, which may be a compressed gas such as nitrogen, or a liquefied gas propellant.

Preferably, pressurized aerosol compositions contain from 0.5 to 5%, for example from 1 to 3.5% by weight, of finely divided active ingredient.

Liquefied gas propellant media are preferably such that the active ingredient does not dissolve therein to a substantial extent.

Suitable liquefied gas propellants which may be employed are dimethyl ether and alkanes containing up to five carbon atoms, for example butane or pentane, or a lower alkyl chloride, eg methyl, ethyl or propyl chlorides. The most suitable liquefied gas propellants are the fluorinated and fluorochlorinated lower alkanes such as are sold under the Registered Trade Mark 'Freon'. The use of the latter type of propellants is a matter of current concern, and they may be replaced by a suitable substitute when such is available. Mixtures of the above mentioned propellants may suitably be employed.

The composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of the sodium salt. A preferred solid anionic surface active agent is sodium dioctyl-sulphosuccinate. We prefer the liquid non-ionic surface-active agent to comprise from 0.1 to 2%, and more preferably from 0.2 to 1%, by weight of the total composition. Such compositions tend to be more physically stable on storage.

Pressurized aerosol compositions may be prepared by mixing the various components at a temperature and pressure at which the propellant is in the liquid phase and the

active ingredient is in the solid phase, and then filled into aerosol canisters by conventional methods.

According to a third aspect of the invention, there is provided a method of symptomatic treatment of cystic fibrosis, which comprises administering a therapeutically effective amount of UTP, or a pharmaceutically acceptable salt thereof, to a patient suffering from such a condition. The preferred mode of administration is by inhalation to the lung.

A suitable dose for administration by inhalation is in the range 1 to 10mg per day, for example 5mg per day.

According to a further aspect of the invention, there is provided the use of UTP, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the symptomatic treatment of cystic fibrosis.

The efficacy of UTP, or a pharmaceutically acceptable salt thereof, in the symptomatic treatment of cystic fibrosis may be enhanced by using in conjunction with drugs having a sodium ion channel blocking effect. A sodium ion channel blocker which may be mentioned is amiloride.

The invention is illustrated by the following Examples.

Example 1

Preparation of a pressurized aerosol composition

Ingredients:

UTP, trisodium salt (mass median diameter 3μm)	0.270
Sorbitan trioleate	0.091
Propellant 114	7.099
Propellant 12	10.649
	18.109

Method:

The sorbitan ester is dispersed in up to half the propellant 12 at -40°C while stirring with a high dispersion mixer. The active ingredient is added to the resulting dispersion and disperses in it. The balance of the propellant 12 is then added at -50°C, followed by the propellant 114 also cooled to -50°C. The resulting mixtures are then filled into vials onto which valves, eg metering valves, are subsequently crimped.

Example 2

Stimulation of chloride ion secretion from tracheal epithelium

It is believed that, *in vivo*, secretion of chloride ion by the epithelium of the airways leads to secretion of water by the tissue, and so to thinning of the mucus. Consequently, the more potent a compound is in the stimulation of chloride ion secretion by the epithelium, the more effective it is likely to be in thinning mucus in the airways.

A portion of rabbit tracheal epithelium was mounted in an Ussing chamber. The chamber was connected via electrodes to a voltage clamp system, which allows the 'short circuit current' to be measured. This short circuit current is equal to the sum of all active ion transport processes taking place in the tissue. In tracheal epithelium the dominant ion transport processes are chloride ion secretion and sodium ion absorption. In order to observe only the chloride ion secretion process, amiloride (a sodium ion channel blocker) is present on the lumenal side of the tissue.

The short circuit current was measured at a variety of ATP and UTP concentrations, and a dose response curve then constructed, allowing ED_{50} values (the concentration at which 50% of the maximum response is observed) to be calculated.

The ED_{50} values of ATP and UTP were found to be $2x10^{-6}M$ and $2x10^{-7}M$ respectively. This suggests that UTP will be substantially more efficacious in thinning mucus in cystic fibrosis patients than ATP.

Claims:

1. A pharmaceutical composition adapted for inhalation to the lungs, comprising UTP, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

2. A composition as claimed in claim 1, which is an aqueous solution for nebulization.

3. A composition as claimed in claim 1, which is a pressurized aerosol composition containing a pharmaceutically acceptable aerosol propellant.

4. A composition as claimed in claim 1, which is a non-pressurized powder composition containing a pharmaceutically acceptable carrier having a mass median diameter of up to 400μm.

5. UTP, or a pharmaceutically acceptable salt thereof, having a mass median diameter in the range 1-10μm.

6. UTP, or a pharmaceutically acceptable salt thereof, as claimed in claim 5, having a mass median diameter in the range 2-4μm.

7. A composition as claimed in claim 3 or claim 4, comprising UTP, or a pharmaceutically acceptable salt thereof, having a mass median diameter as claimed in claim 5 or claim 6.

8. The use of UTP, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the symptomatic treatment of cystic fibrosis.

9. A method of symptomatic treatment of cystic fibrosis, which comprises administering a therapeutically effective amount of UTP, or a pharmaceutically acceptable salt thereof, to a patient suffering from such a condition.